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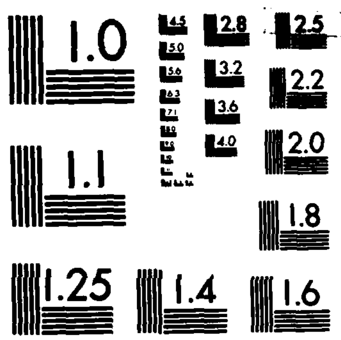

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TESTS CONDITIONAL ON IMBALANCE WITH BIASED COIN DESIGNS

by

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Distributional properties of the treatment assignment variables $T_1, \ldots, T_n$ under Efron's (1971) biased coin design are derived. These properties are conditional on the terminal imbalance of the treatment allocation. Recursive procedures are presented for obtaining the conditional moments of $T_1, \ldots, T_n$. Based on these results, large-sample test statistics are proposed for the randomization test of the null hypothesis of no treatment difference. In contrast to Efron's test statistic, the approximations herein proposed are applicable when there is a treatment allocation imbalance.

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1. INTRODUCTION

Consider a clinical trial to compare the efficacies of treatments A and B. It is typical in these trials that patient arrival and treatment assignment is sequential. To obtain a balanced or nearly balanced treatment allocation, without increasing unacceptably experimental biases, Efron (1971) proposed a biased coin treatment allocation. Let T_1, T_2, ... denote the assignment variables with $T_i = 0$ or 1 depending on whether the i^{th} patient receives treatment A or B, respectively. With $D_0 = 0$, define for i = 1, 2, ...

$$D_i = 2\sum_{j=1}^{i} T_j - i\,. \tag{1.1}$$

Under Efron's (1971) biased coin design with bias $p(\frac{1}{2} < p < 1)$, hereon abbreviated BCD(p), the probability that the $(i+1)^{th}$ patient receives B is p, ½, $q = 1 - p$ according to whether D_i <, =, > 0, respectively. Wei (1977, 1978) generalized this design by allowing the $(i+1)^{th}$ patient's assignment probabilities to depend on i and D_i.

We confine our attention to a clinical trial where the treatments are assigned to n patients via the BCD(p). In Section 2 distributional properties of $T_1, \ldots, T_n$, conditional on D_n, are presented. Procedures for computing approximations to the conditional moments of $T_1, \ldots, T_n$ are given in Section 3. In Section 4 we discuss the relevance of the results in Sections 2 and 3 in relation to the randomization test of H_0, the null hypothesis of no treatment difference. We consider test statistics of the form

$$S_n = \sum_{i=1}^{n} a_i T_i\,, \tag{1.2}$$

where $a_1, \ldots, a_n$ is a nonrandom sequence of scores associated with the sequence of patient responses $x_1, \ldots, x_n$. The two-sided version of the randomization test thus rejects H_0 if the observed S_n is either "too small" or "too large".

In deciding whether a test statistic is too small or too large, Cox (1982) recommended that the reference randomization distribution should be taken over those treatment allocations with the same or nearly the same terminal imbalance as the observed allocation. In accordance with Cox's suggestion, the results of Sections 2 and 3 are conditional on D_n. Note however that some authors use the unconditional randomization distribution of S_n(see Smythe and Wei (1983) and Smith (1984)).

In his doctoral dissertation, E. Peña derived a recursion procedure for obtaining the exact randomization distribution of S_n, conditional on $D_n = m$. This procedure enables one to perform exact significance tests of H_0, but for large sample sizes the computer time required to implement the recursion may not be acceptable. In Section 4 we therefore suggest an alternative test procedure based on approximating the distribution of S_n by the normal distribution. In Section 5 a computer simulation is used to assess the adequacy of the normal approximation for n = 51 and n = 101.

Efron (1971) presented approximations to the conditional parameters of S_n, and suggested approximating the conditional randomization distribution of S_n by the normal distribution. However, in a simulation study, Halpern and Brown (1986) indicated that Efron's approximations are inadequate in the presence of treatment allocation imbalance. The results in Section 2 offer a theoretical explanation for this inadequacy, and in conjunction with the results of Section 3 provide improved approximations to the conditional moments of S_n whenever $D_n \neq 0$.

2. DISTRIBUTIONAL PROPERTIES OF $T_1, \ldots, T_N$

Let Z be the set of integers, Z_+ the set of positive integers, and set $Z_+^0 = Z_+ \cup \{0\}$. By the defining property of the BCD(p), the process $D_0, D_1, \ldots$ in (1.1) is a homogeneous Markov chain with state space Z having stationary transition probabilities

$$P_{i,j} = \mathrm{pr}(D_1=j|D_0=i), \qquad j \in Z,\ i \in Z$$

$$= \begin{cases} \frac{1}{2} & \text{if } j = \pm 1,\ i = 0 \\ p & \text{if } (j=i+1, i<0) \text{ or } (j=i-1, i>0) \\ q & \text{if } (j=i-1, i<0) \text{ or } (j=i+1, i>0) \\ 0 & \text{otherwise.} \end{cases} \tag{2.1}$$

The n^{th} order transition probabilities of this chain will be denoted by $\{P^n_{i,j},\ i\epsilon Z,\ j\epsilon Z\}$, and the stationary distribution probabilities by $\{\pi_j,\ j\epsilon Z\}$. These stationary probabilities are

$$\pi_0 = (p-q)/(2p) \quad \text{and} \quad \pi_j = \pi_{-j} = (p-q)/(4p^2)(q/p)^{j-1}, \qquad j \in Z_+. \tag{2.2}$$

In order to maintain continuity in the presentation of the results, all proofs are deferred to Section 6.

<u>Theorem 2.1:</u> If $m \in Z$ with $P^n_{0,m} > 0$, then conditional on $D_n = m$,

(i) T_{2i-1} and T_{2i} are exchangeable, and

(ii) T_{2i} and T_{2i+1} are exchangeable whenever $m = 0$, for $i = 1, \ldots, [n/2]$, where $[k]$ denotes the greatest integer $\le k$.

Let V and W be random variables. Recall that $V(\overset{d}{\le}, \overset{d}{=}, \overset{d}{\ge})W$ if for every real number v, $\mathrm{pr}(V\le v)(\ge,=,\le)\ \mathrm{pr}(W\le v)$, respectively.

<u>Corollary 2.1:</u> If $m \in Z$ with $P^n_{0,m} > 0$, then conditional on $D_n = m$, $(T_1, \ldots, T_{2i-2}, T_{2i-1}, T_{2i}, T_{2i+1}, \ldots, T_n) \overset{d}{=} (T_1, \ldots, T_{2i-2}, T_{2i}, T_{2i-1}, T_{2i+1}, \ldots, T_n)$ for every $i = 1, \ldots, [n/2]$.

On the otherhand, it is <u>not</u> true that, conditional on $D_n = 0$, $(T_1, \ldots, T_{2i-1}, T_{2i}, T_{2i+1}, T_{2i+2}, \ldots, T_n) \stackrel{d}{=} (T_1, \ldots, T_{2i-1}, T_{2i+1}, T_{2i}, T_{2i+2}, \ldots, T_n)$ for $i = 1, \ldots, [n/2]$ as the following example illustrates.

Example 2.1: Under the BCD(p), $pr(T_1=1, T_2=0, T_3=1, T_4=0 | D_0=0, D_4=0) \neq pr(T_1=1, T_2=1, T_3=0, T_4=0 | D_0=0, D_4=0)$.

However, aside from Theorem 2.1 (ii), we have the following results for the pairs (T_{2i}, T_{2i+1}), $i = 1, \ldots, [n/2]$.

Theorem 2.2: If $m \in Z$ with $P^n_{0,m} > 0$ then, conditional on $D_n = m$, $T_{2i} (\stackrel{d}{\leq}, \stackrel{d}{=}, \stackrel{d}{\geq}) T_{2i+1}$ according to whether $m(>,=,<)\, 0$, respectively, for $i = 1, \ldots, [n/2]$.

Corollary 2.1 implies that the randomization distribution of S_n, conditional on $D_n = m$, is invariant with respect to permutations of members in the doubletons $\{a_{2i-1}, a_{2i}\}$ for $i = 1, \ldots, [n/2]$. Thus there are at most $\Pi\, C(n-2i,2)$ permutations of $a_1, \ldots, a_n$ that give distinct conditional randomization distributions for S_n, where Π represents the product from $i = 0$ to $i = [n/2]$ and $C(b,a)$ denotes the number of combinations of a objects taken from b distinct objects. Unfortunately, this bound increases rapidly with n, making it impractical to construct tables of critical values for the conditional randomization distribution of S_n.

That the conditional randomization distribution of S_n depends on the particular order of $a_1, \ldots, a_n$ under the BCD(p) is in contrast with the case where treatments are assigned via complete randomization, or equivalently via BCD(½). In the latter situation, $T_1, \ldots, T_n$ are exchangeable, conditional on $D_n = m$, and hence the conditional randomization distribution of S_n is invariant with respect to permutations of $a_1, \ldots, a_n$.

Let $\mu^n_{i,m} = E(T_i | D_0=0, D_n=m)$ for $i = 1, \ldots, n$ and $\sigma^n_{ij,m} = cov(T_i, T_j | D_0=0, D_n=m)$ for $i,j = 1, \ldots, n$. An immediate consequence of Theorems 2.1 and 2.2 is:

Corollary 2.2: If $m \in Z$ with $P^n_{0,m} > 0$, then for $i = 1, \ldots, [n/2]$,

(i) $\mu^n_{2i-1,m} = \mu^n_{2i,m}$, and

(ii) $\mu^n_{2i,m}$ $(\leq,=,\geq)$ $\mu^n_{2i+1,m}$ if $m(>,=,<)0$, respectively.

Furthermore, since

$$\mu^n_{1,m} = P^{n-1}_{1,m} / (P^{n-1}_{1,m} + P^{n-1}_{-1,m}), \tag{2.3}$$

then $\mu^n_{1,m}$ $(>,=,<)\frac{1}{2}$ according to whether $m(>,=,<)0$. By Corollary 2.2 and using the relation $\sigma^n_{ii,m} = \mu^n_{i,m}(1-\mu^n_{i,m})$ it follows that:

Corollary 2.3: If $m \in Z$ with $P^n_{0,m} > 0$, then for $i = 1, \ldots, n$,

(i) $\mu^n_{i,m}(>,=,<)\frac{1}{2}$ if $m(>,=,<)0$, respectively, and

(ii) $\sigma^n_{ii,m}(=,<)\frac{1}{4}$ if $m(=,\neq)0$, respectively.

With the object of evaluating the conditional mean of S_n, it is of interest to know if the $\mu^n_{i,m}$'s can be well-approximated by $\frac{1}{2}\{1+(m/n)\}$, the latter being the conditional mean of each T_i under complete randomization. To resolve this question, we resort to limiting values. Since D_0, D_1, ... is a Markov chain of period 2, then $P^{2n}_{0,2m}$ and $P^{2n-1}_{0,2m-1}$ converge to $2\pi_{2m}$ and $2\pi_{2m-1}$, respectively. Using (2.2) and (2.3) it follows that $\mu^n_{1,m}$ converges to $\frac{1}{2}$ as n tends to infinity. By a similar argument, $\mu^n_{n,m}$ can be shown to converge to p, $\frac{1}{2}$ or q depending on whether m >, =, or < 0, respectively. Therefore, if $m \neq 0$, the absolute difference between $\mu^n_{n,m}$ and $\mu^n_{1,m}$ tends to $p - \frac{1}{2}$ as n increases. Consequently, it is our view that approximating the $\mu^n_{i,m}$'s by $\frac{1}{2}\{1 + (m/n)\}$ is not advisable. The inadequacy of these approximations is further illustrated by results of the simulation in Section 5.

3. CONDITIONAL MEANS AND COVARIANCES

In this section we present recursive procedures for computing the conditional means and covariances of $T_1, \ldots, T_n$. For ease of implementation, but at the cost of obtaining only approximate results, we follow Efron (1971) and assume that the process $D_0, D_1, \ldots$ is at its stationary state. The results below thus pertain to the process $D_0, D_1, \ldots$ satisfying

$$\mathrm{pr}(D_0=j) = \pi_j, \quad j \in Z, \tag{3.1}$$

where $\{\pi_j, j\in Z\}$ are given in (2.2).

Theorem 3.1: If (3.1) is satisfied, then for $m \in Z$

(i) $\mu^n_{i,m} = \mu^{n-i+1}_{1,m}$, $i = 1, \ldots, n;\ \ n \in Z_+$, and

(ii) $\sigma^n_{ii+j,m} = \sigma^{n-i+1}_{11+j,m}$, $j = 1, \ldots, n - i;\ \ i = 1, \ldots, n - 1;\ \ n \in Z_+$.

Theorem 3.1 implies that to compute $\mu^n_{i,m}$ for $i = 1, \ldots, n$, one must simply obtain $\mu^k_{1,m}$ for $k = 1, \ldots, n$; and, similarly, for the covariances. The following theorems provide methods for obtaining $\mu^k_{1,m}$ and $\sigma^k_{11+j,m}$ for $k = 1, \ldots, n$.

Theorem 3.2: If (3.1) is satisfied, then

$$\mu^k_{1,m} = \pi^{-1}_m L^k_m$$

where $\{L^k_m\}$ satisfy the recursion equation

$$L^k_m = \gamma_{m-1} L^{k-1}_{m-1} + (1-\gamma_{m+1})L^{k-1}_{m+1}, \quad k = 2, 3, \ldots$$

with initial and boundary conditions $L^1_m = \pi_{m-1}\gamma_{m-1}$, $m \in Z$, and where $\gamma_m = p, \frac{1}{2}, q$ according to whether $m(<,=,>)0$, respectively.

Theorem 3.3: If (3.1) is satisfied, then

$$E(T_1 T_{1+j} \mid D_k=m) = \pi_m^{-1} L_m^k, \quad j = 1, \ldots, n-1$$

where $\{L_m^k\}$ satisfy the recursion equation

$$L_m^k = \gamma_{m-1} L_{m-1}^{k-1} + (1-\gamma_{m+1}) L_{m+1}^{k-1}, \; k = 2+j, 3+j, \ldots$$

with initial and boundary conditions $L_m^{1+j} = \gamma_{m-1}\pi_{m-1}\mu_{1,m-1}^j$, $m \in Z$.

The conditional covariances are then obtained through the relation

$$\sigma_{11+j,m}^k = E(T_1 T_{1+j} \mid D_k=m) - \mu_{1,m}^k \mu_{1,m}^{k-j}$$

and Theorem 3.1.

To illustrate the adequacy of these approximations for a moderate sample size, the exact and approximate conditional means of $T_1, \ldots, T_n$ for $n = 51$, $p = 2/3$ and $m = 1$, 3 and 5 were computed. Exact values were obtained using procedures in Peña's dissertation. The results are summarized in Table 1. Notice that for practical purposes it suffices to use the approximate means (and variances) for this value of n and p. The simulation results in the next section indicate however that when the approximate covariances are used to compute the standard deviation of S_n, this could lead to overestimation of the exact standard deviation of S_n for some score sequences $a_1, \ldots, a_n$.

4. LARGE-SAMPLE TEST PROCEDURES

With $a_i = x_i - \bar{x}$ in (1.2) Efron (1971) standardized S_n as

$$Z_1 = \frac{\sum_{i=1}^n a_i\{T_i - \tfrac{1}{2}(1+\frac{m}{n})\}}{\{\tfrac{1}{4}\sum_{i=1}^n a_i^2 + \sum\sum_{i\neq j} a_i a_j \sigma_{ij}\}^{\frac{1}{2}}}, \tag{4.1}$$

Table 3.1. Summary of exact and approximate conditional means $\mu_{i,m}^{n}$ for n = 51, p = $\frac{2}{3}$ and m = 1, 3 and 5

i	m = 1		m = 3		m = 5	
	Exact	Approximate	Exact	Approximate	Exact	Approximate
1	.5002	.5002	.5008	.5009	.5024	.5027
3	.5002	.5002	.5011	.5011	.5031	.5032
5	.5002	.5002	.5013	.5013	.5037	.5038
7	.5003	.5003	.5016	.5016	.5045	.5044
9	.5003	.5003	.5019	.5018	.5053	.5052
11	.5004	.5004	.5022	.5022	.5063	.5062
13	.5005	.5005	.5027	.5026	.5075	.5073
15	.5006	.5006	.5032	.5031	.5089	.5086
17	.5007	.5007	.5038	.5037	.5106	.5103
19	.5008	.5008	.5046	.5044	.5126	.5122
21	.5010	.5010	.5055	.5053	.5150	.5146
23	.5012	.5012	.5066	.5065	.5179	.5174
25	.5015	.5015	.5080	.5078	.5214	.5209
27	.5018	.5018	.5098	.5096	.5257	.5251
29	.5023	.5022	.5120	.5117	.5309	.5302
31	.5028	.5028	.5147	.5145	.5373	.5366
33	.5035	.5035	.5182	.5180	.5451	.5444
35	.5045	.5044	.5228	.5225	.5548	.5540
37	.5058	.5057	.5288	.5285	.5668	.5659
39	.5075	.5075	.5367	.5364	.5817	.5806
41	.5101	.5100	.5476	.5472	.5999	.5987
43	.5139	.5138	.5628	.5624	.6217	.6203
45	.5200	.5199	.5848	.5844	.6462	.6447
47	.5309	.5309	.6178	.6173	.6683	.6667
49	.5556	.5556	.6672	.6667	.6683	.6667
51	.6668	.6667	.6672	.6667	.6683	.6667

where $\sigma_{ij} = \mathrm{cov}(T_i, T_j)$ denotes the unconditional covariance between T_i and T_j. He suggested approximating the conditional randomization distribution of Z_1 by the standard normal distribution. Efron assumed that there was complete balance in the treatment allocation, that is, $D_n = 0$. In that case Z_1 has conditional mean 0 but its conditional variance may not be 1.0 since in the denominator of (4.1) σ_{ij} was used instead of $\sigma^n_{ij,m}$. Furthermore, if $D_n = m \neq 0$, Corollary 2.3 shows that Z_1 has a nonzero conditional mean and a conditional variance that will tend to be smaller than 1.0. Thus, assuming that the distribution of Z_1 is normal, the standard normal approximation may go awry. This offers a theoretical explanation for the simulation-based conclusion of Halpern and Brown (1986) that the standard normal approximation to Z_1 is inadequate in the presence of treatment imbalance.

With the ability to compute the conditional means and covariances of the T's using results of Section 3, we propose the use of the test statistic

$$Z_2 = \frac{\sum_{i=1}^{n} a_i (T_i - \mu^n_{i,m})}{\{\sum_{i=1}^{n} a_i^2 \sigma^n_{ii,m} + \sum_{i \neq j}\sum a_i a_j \sigma^n_{ij,m}\}^{\frac{1}{2}}}, \tag{4.2}$$

where the $a_1, \ldots, a_n$ are standardized to satisfy $\sum_{i=1}^{n} a_i = 0$. If the standard normal distribution is then used to approximate the distribution of Z_2, the α-level two-sided randomization test rejects H_0 if $|Z_2| > z_{\alpha/2}$, where $z_{\alpha/2}$ is the $(1-\alpha/2)100\%$ percentile of the standard normal distribution.

Efron (1971) showed that when the sequence $a_1, \ldots, a_n$ is noisy, the covariance term in (4.1) given by

$$K = \sum_{i \neq j}\sum a_i \, a_j \, \sigma_{ij} \tag{4.3}$$

is near 0. We expect the covariance term in (4.2) given by

$$K' = \sum_{i \neq j}\sum a_i a_j \sigma^n_{ij,m} \tag{4.4}$$

to have roughly the same behaviour as K. If the score sequence is noisy we thus prefer to use the computationally simpler test statistic

$$Z_3 = \frac{\sum_{i=1}^{n} a_i (T_i - \mu^n_{i,m})}{\{\sum_{i=1}^{n} a_i^2 \sigma^n_{ii,m}\}^{1/2}}$$

rather than Z_2.

We are not able to provide a theoretical justification for the standard normal approximation to the conditional randomization distribution of Z_1, Z_2, and Z_3. This problem of proving that the conditional randomization distributions converge in distribution to the normal distribution is a difficult theoretical problem, moreso under the BCD(p). Under Wei's (1978) adaptive biased coin design, Wei, Smythe and Smith (1986) approached this problem by proving the joint asymptotic normality of (S_n, D_n), and then conjecturing that S_n, conditional on D_n, is asymptotically normal. However, Smythe and Wei (1983) pointed out that the unconditional distribution of $S_n = \sum_{i=1}^{n} a_{ni} T_i$ under the BCD(p) may not be asymptotically normal. The approach of Wei, Smythe, and Smith may not therefore work for our problem since (S_n, D_n) may not be jointly asymptotically normal.

A computer simulation was performed to examine the adequacy of the normal approximation to the conditional randomization distributions of Z_1, Z_2, and Z_3. Details of this study are discussed in the next section.

5. A SIMULATION STUDY

The simulation was performed at the Florida State University Computing Center on a Control Data Cyber 730 computer. The uniform random number generator used was the intrinsic routine RANF.

Two sample sizes, $n = 51$ and $n = 101$, were considered in the simulation, and the scores in (1.2) were set to $a_i = \mathrm{rank}(x_i) - (n+1)/2$. The covariance quantity K in (4.3) was set to 0. For each sample size, five score sequences were considered, and as a measure of the noise of each sequence their respective correlation coefficients with 1, 2, ..., n were computed. A low absolute correlation coefficient indicates a high degree of noise. These correlation coefficients are summarized in Table 2.

Table 2. Correlation coefficients for the 10 rank sequences in the simulation study.

Sample Size, n	Sequence Number				
	1	2	3	4	5
51	0.0724	0.1919	0.3719	0.7252	1.00
101	-0.1988	0.0071	0.3244	0.6827	1.00

For each score sequence, 10000 replicates of assignment variates $t_1, \ldots, t_n$ were generated via the BCD(p) with $p = 2/3$. For each of these replicates, the values of Z_1, Z_2, and Z_3 were computed, with the conditional means and covariances of $T_1, \ldots, T_n$ approximated by the procedures in Section 3. After stratifying the 10000 replicates according to their value of $D_n = m$, the mean, standard deviation, percentages of values greater than 1.645, 1.96, and 2.33 of Z_1, Z_2, and Z_3 were determined. The results are summarized in Table 3 for $n = 51$, and in Table 4 for $n = 101$. Those values that are superscripted by one or two asterisks are significantly different, based on the classical Z-test, from what is expected under the standard normal distribution at level 0.05 or 0.01, respectively.

Tables 3 and 4 indicate that the adequacy of the standard normal approximation depends on the degree of noise of the score sequence. The more noise there is in the sequence, the better the approximation. Notice that for sequences 1 and 2 which are the noisiest sequences, the percentages of values of Z_1, Z_2 and Z_3 greater than 1.645, 1.96, and 2.33, for most values of m, are statistically consistent with the 5.0, 2.5, and 1.0 percent that could be expected under the standard normal.

For almost all cases, the means of Z_2 and Z_3 are statistically consistent with 0; in contrast, the means of Z_1 are, for most cases, statistically different from 0. This supports our earlier observations that the approximations to the $\mu^n_{i,m}$'s in Section 3 are good, and that $\frac{1}{2}\{1+(m/n)\}$ should not be substituted for the $\mu^n_{i,m}$'s. Note also that the departure from 0 of the mean of Z_1 increases as the treatment allocation imbalance increases. Aside from that, as n increases, the mean of Z_1 tends to increase or decrease according to whether the correlation is positive or negative, respectively.

The behaviours of Z_2 and Z_3 for sequences 1 and 2 are almost identical, implying that the covariance term K' in (4.4) is near 0. Their standard deviations become more different however, as we go along sequences 3, 4 and 5 for both values of n. This implies that when the score sequence is noisy, the covariance term K' should not be ignored, and Z_2 should be the preferred test statistic. On the otherhand, the standard deviations of Z_1 and Z_3 are almost identical for all cases.

We expect Z_2's standard deviation to be 1.0; however, the observed standard deviations of Z_2 for sequences 4 and 5 are significantly lower than 1.0. The increase in sample size from n = 51 to n = 101 did not improve the approximation. This indicates that the approximations to the covariances given in Section 3 lead to an overestimate of K' in (4.4). Consequently, if Z_2 is computed using the approximations in Section 3, and the standard normal is used to approximate the distribution of Z_2, the randomization test which rejects H_0 if $|Z_2| > z_{\alpha/2}$ will tend to be a conservative test for non-noisy score sequences.

Table 3. Means, standard deviations, percentages greater than 1.645, 1.96, and 2.33 of Z_1, Z_2, and Z_3 for n = 51

Score Sequence (Correlation)	$D_{51}=m$	Number of Replicates	Mean			Standard Deviation			% > 1.645			% > 1.96			% > 2.33		
			Z_1	Z_2	Z_3	Z_1	Z_2	Z_3	Z_1	Z_2	Z_3	Z_1	Z_2	Z_3	Z_1	Z_2	Z_3
	-5	239	-.05	-.04	-.04	.97	.98	.98	4.60	5.02	5.02	2.93	2.93	2.93	.84	.84	.84
	-3	943	-.06*	0	0	1.00	1.00	1.00	4.03	4.45	4.45	1.48**	1.80	1.80	.74	.74	.74
1	-1	3756	-.04**	0	0	.98*	.99	.99	4.53	5.11	4.95	2.02*	2.26	2.26	.93	1.09	.99
(0.0724)	1	3719	.06**	.02	.02	.98*	.98*	.98*	5.57	5.06	5.06	2.69	2.64	2.53	1.21	1.08	1.08
	3	922	.09**	.04	.04	.97	.97	.98	5.97	5.31	5.31	2.93	2.60	2.60	.76	.54*	.76
	5	252	.19**	.18**	.18**	.95	.96	.96	7.14	7.14	7.14	3.57	3.57	3.57	.79	.79	.79
	-5	235	-.06	.10	.10	.95	.97	.96	2.55*	5.11	5.11	1.28*	2.55	2.55	.85	.85	.85
	-3	899	-.09**	.02	.02	.98	1.00	.99	4.12	4.78	4.67	1.89	2.89	2.67	.33**	.44**	.44**
2	-1	3830	-.01	-.01	-.01	.99	1.00	.99	4.73	4.91	4.73	2.09*	2.27	2.09*	.89	.91	.89
(0.1919)	1	3668	0	.01	.01	.98*	.99	.98*	4.61	4.83	4.61	1.96**	2.21	2.07*	.55**	.65**	.55**
	3	971	.12**	.01	.01	1.01	1.03	1.02	6.80	5.97	5.77	4.12**	3.60*	3.30	1.75*	1.54	1.44
	5	240	.19**	.03	.03	1.03	1.05	1.04	7.92*	6.25	6.25	4.17	3.33	3.33	2.50	1.67	1.67
	-5	240	-.29**	-.06	-.05	.97	1.01	.98	1.25**	3.33	2.92*	0**	1.67	.42**	0**	0**	0**
	-3	929	-.15**	.02	.02	.91**	.96**	.91**	2.48**	4.95	3.66*	.54**	2.37	1.72*	.11**	.32**	.11**
3	-1	3817	-.08**	0	0	.93**	.97**	.93**	2.93**	4.43*	3.62**	1.10**	1.89**	1.47**	.34**	.63**	.45**
(0.3719)	1	3711	.08**	0	.01	.93**	.97**	.93**	4.82	4.82	4.04**	2.05*	2.24	1.86**	.62**	.78	.49**
	3	935	.20**	.04	.04	.92**	.97	.93**	6.52*	5.24	4.06	2.67	2.14	1.60*	.96	.86	.75
	5	218	.36**	.12*	.12*	.99	1.04	1.00	8.71*	7.33	5.04	5.04*	3.67	2.75	2.29	1.38	.92
	-5	244	-.48**	.01	.01	.83**	.97	.84**	1.23**	4.92	3.28	.82**	2.46	1.23*	.41	1.23	.82
	-3	934	-.39**	-.03	-.03	.79**	.95**	.80**	.64**	4.18	2.25**	0**	2.25	.75**	0**	.75	0**
4	-1	3785	-.16**	-.01	-.01	.76**	.93**	.76**	.92**	3.70**	1.45**	.21**	1.80**	.42**	0**	.61**	0**
(0.7252)	1	3739	.17**	.04**	.03**	.75**	.93**	.76**	2.75**	4.44*	1.79**	.72**	2.09*	.37**	.19**	.51**	.05**
	3	911	.38**	.02	.02	.79**	.96	.80**	5.71	4.39	2.09**	2.41	2.09	.66**	.66	.77	.44**
	5	254	.51**	.03	.03	.82**	.96	.83**	7.87*	5.12	2.76*	4.72*	1.97	1.18*	1.18	.39	.39
	-5	236	-.71**	-.05	-.03	.62**	.91*	.64**	0**	6.78	2.54**	0**	5.08*	1.27*	0**	3.39*	0**
	-3	932	-.51**	-.03	-.02	.48**	.79**	.49**	.32**	2.58**	.64**	.11**	1.61*	.43**	.11**	.86	.21**
5	-1	3732	-.20**	-.01	-.01	.43**	.76**	.43**	.13**	2.47**	.21**	.11**	1.13**	.11**	.03**	.59**	.08**
(1.00)	1	3770	.18**	-.02	-.01	.44**	.79**	.45**	.32**	1.99**	.08**	.05**	.90**	0**	0**	.56**	0**
	3	961	.49**	.01	.01	.49**	.80**	.49**	.73**	1.56**	.31**	.31**	.62**	0**	0**	.31**	0**
	5	209	.74**	.09*	.06	.52**	.75**	.53**	2.87*	1.91**	.96**	1.44	1.44	0**	.48	.96	0**

*Significantly different from what is expected under the standard normal at α = 0.05.

**Significantly different from what is exepcted under the standard normal at α = 0.01.

<u>Table 4.</u> Means, standard deviations, percentages greater than 1.645, 1.96, and 2.33 of Z_1, Z_2, and Z_3 for n = 101

Score Sequence (Correlation)	D_{101}-m	Number of Replicates	Mean			Standard Deviation			% > 1.645			% > 1.96			% > 2.33		
			Z_1	Z_2	Z_3	Z_1	Z_2	Z_3	Z_1	Z_2	Z_3	Z_1	Z_2	Z_3	Z_1	Z_2	Z_3
1 (-0.1988)	-5	221	.20**	-.01	-.01	.93	.94	.93	4.52	3.62	3.62	3.62	1.81	1.81	.91	.45	0**
	-3	981	.17**	.03	.03	.99	1.00	.99	7.24**	5.10	4.89	3.06	2.04	1.94	.92	.71	.61
	-1	3698	.03*	0	0	1.01	1.02	1.01	5.38	5.32	4.98	2.89	2.87	2.70	1.27	1.22	1.16
	1	3764	-.03*	-.01	-.01	.99	1.00	.99	4.68	5.13	4.97	2.60	2.87	2.82	.98	1.06	1.04
	3	952	-.21**	-.06*	-.06*	1.03	1.04*	1.03	2.73**	4.73	4.62	1.26**	2.00	2.00	.42**	.63	.63
	5	220	-.28**	-.07	-.07	1.05	1.07	1.06	5.45	6.82	6.82	2.73	4.55	4.55	1.82	2.27	2.27
2 (0.0071)	-5	240	.05	-.03	-.03	.97	.97	.98	5.83	4.58	4.58	2.50	1.25*	1.25*	.83	.42	.83
	-3	926	.07*	.01	.01	1.00	1.00	1.01	5.62	4.99	5.18	2.59	2.38	2.38	.86	.76	.76
	-1	3738	.03*	0	0	1.01	1.00	1.01	5.56	5.24	5.32	2.94	2.57	2.68	1.07	.86	.88
	1	3739	-.04**	0	0	1.01	1.00	1.01	4.39*	4.71	4.84	2.01*	2.06*	2.17	.86	.88	.91
	3	939	-.10**	-.04	-.04	1.03	1.02	1.03	5.22	5.86	5.96	3.19	3.41	3.51*	1.38	1.38	1.38
	5	255	-.09	-.02	-.02	.98	.98	.98	2.75*	3.14*	3.14*	.39**	1.18*	1.18*	0**	0**	0**
3 (0.3244)	-5	216	-.18**	.02	.02	.95	.98	.96	2.31**	5.56	4.63	.46**	2.31	1.85	0**	.46	.46
	-3	958	-.10**	0	0	.95*	.98	.96*	2.61**	4.28	3.86*	1.25**	1.98	1.77*	.42**	.94	.89
	-1	3779	-.04**	-.01	-.01	.98*	1.00	.98*	4.00**	4.79	4.34*	1.98*	2.28	2.17	.85	1.01	.93
	1	3791	.06**	.02	.02	.97**	.99	.97**	4.91	4.93	4.62	2.61	2.77	2.40	1.06	1.11	.95
	3	889	.15**	.06*	.05	.95*	.97	.95*	5.85	5.40	5.17	3.82*	3.60*	3.26	1.80*	1.35	1.12
	5	221	.18**	-.02	-.02	.98	1.01	.99	7.69	5.88	5.88	4.52	3.62	3.17	1.81	1.36	1.36
4 (0.6827)	-5	247	-.44**	-.06	-.05	.78**	.97	.78**	0**	2.02**	0**	0**	0**	0**	0**	0**	0**
	-3	955	-.28**	-.01	-.01	.76**	.94**	.76**	.31**	3.46**	1.47**	0**	1.68*	.21**	0**	.52*	0**
	-1	3803	-.12**	0	0	.77**	.96**	.77**	1.05**	4.37*	1.58**	.39**	2.02*	.55**	.11**	.74**	.13**
	1	3671	.12**	.01	.01	.76**	.94**	.76**	2.23**	4.47	1.36**	.49**	1.83**	.44**	.16**	.49**	.11**
	3	942	.27**	0	0	.78**	.97	.79**	4.14	4.56	1.70**	1.49**	2.12	.64**	.64	.96	.32**
	5	219	.37**	-.02	-.02	.73**	.90*	.73**	5.94	4.57	.91**	.91**	.91**	.45**	.46	.91	0**
5 (1.00)	-5	233	-.66**	.02	.01	.28**	.63**	.28**	0**	2.15**	0**	0**	.86**	0**	0**	.43	0**
	-3	956	-.42**	.01	.01	.27**	.65**	.27**	0**	1.67**	.10**	0**	.94**	0**	0**	.63	0**
	-1	3808	-.15**	.01	0	.27**	.67**	.27**	.03**	1.52**	.03**	0**	.81**	.03**	0**	.53**	0**
	1	3727	.15**	-.01	0	.28**	.69**	.28**	.03**	1.61**	0**	0**	.83**	0**	0**	.51**	0**
	3	863	.44**	.02	.01	.30**	.71**	.30**	.35**	1.85**	.12**	.12**	1.51**	0**	0**	1.27	0**
	5	246	.66**	-.02	-.01	.34**	.77**	.34**	.41**	1.63**	0**	0**	.41**	0**	0**	.41	0**

*Significantly different from what is expected under the standard normal at α = 0.05.

**Significantly different from what is expected under the standard normal at α = 0.01.

6. PROOFS

Before proving the theorems of Sections 2 and 3 we state the following results which were proved in Peña's dissertation.

<u>Lemma 6.1:</u> The process D_0, D_1, ... is symmetric in the sense that

$$\text{pr}\{\bigcap_{i=1}^{n}(D_i=d_i)|D_0=d_0\} = \text{pr}\{\bigcap_{i=1}^{n}(D_i=-d_i)|D_0=-d_0\}$$

for every d_0, ..., d_n with $d_i \in Z$.

<u>Corollary 6.1:</u> $P^n_{i,j} = P^n_{-i,-j}$, $i \in Z$, $j \in Z$, $n \in Z^0_+$.

<u>Lemma 6.2:</u> If $x,y \in \{0,1\}$ and j, $k \in Z$, then

(i) $\alpha(x,y,j,k) = 0$ whenever j and k are even,

(ii) $\alpha(x,y,j,k) = 0$ whenever j and k are odd and of opposite signs, and

(iii) $\alpha(x,y,j,k) = \alpha(1-x,1-y,-j,-k)$,

where $\alpha(x,y,j,k) = \text{pr}(T_1=x,T_2=y|D_0=j,D_2=k) - \text{pr}(T_1=y,T_2=x|D_0=j,D_2=k)$.

<u>Proof of Theorem 2.1:</u> Let x and y take arbitrary values in $\{0,1\}$. To prove (i), note that $\text{pr}(T_{2i-1}=x,T_{2i}=y|D_0=0,D_n=m) = E_{0,m}\,\text{pr}(T_{2i-1}=x,T_{2i}=y|D_0=0,D_{2i-2},D_{2i},D_n=m)$ where $E_{0,m}$ denotes expectation conditional on $D_0 = 0$, $D_n = m$. By the Markov property of D_0, D_1, ... it follows that $\text{pr}(T_{2i-1}=x,T_{2i}=y|D_0=0,D_n=m) = E_{0,m}\,\text{pr}(T_{2i-1}=x,$ $T_{2i}=y|D_{2i-2},D_{2i})$. To complete the proof it suffices to show that, for j and k even,

$$\text{pr}(T_{2i-1}=x,T_{2i}=y|D_{2i-2}=j,D_{2i}=k) = \text{pr}(T_{2i-1}=y,T_{2i}=x|D_{2i-2}=j,D_{2i}=k).$$

By the homogeneity of D_0, D_1, ... this reduces to showing that, for j and k even,

$$\text{pr}(T_1=x,T_2=y|D_0=j,D_2=k) = \text{pr}(T_1=y,T_2=x|D_0=j,D_2=k).$$

Using Lemma 6.2(i), part (i) of Theorem 2.1 follows.

To prove (ii), note that $pr(T_{2i}=x,T_{2i+1}=y|D_0=0,D_n=m) = E_{0,m}\, pr(T_{2i}=x,$ $T_{2i+1}=y|D_0=0,D_{2i-1},D_{2i+1},D_n=m)$, which by the Markov property of D_0, D_1, ... becomes $pr(T_{2i}=x,T_{2i+1}=y|D_0=0,D_n=m) = E_{0,m}\, pr(T_{2i}=x,T_{2i+1}=y|D_{2i-1},D_{2i+1})$. To complete the proof of (ii) it remains to show that $\beta = E_{0,m}\{pr(T_{2i}=x,T_{2i+1}=y|D_{2i-1},D_{2i+1})$ $- pr(T_{2i}=y,T_{2i+1}=x|D_{2i-1},D_{2i+1})\} = 0$. By expanding the expectation and noting that D_{2i-1} and D_{2i+1} take odd integer values only, we have

$$\beta = \sum_j \sum_k pr(D_{2i-1}=j,D_{2i+1}=k|D_0=0,D_n=m) \cdot \{pr(T_{2i}=x,T_{2i+1}=y|D_{2i-1}=j,D_{2i+1}=k)$$
$$- pr(T_{2i}=y,T_{2i+1}=x|D_{2i-1}=j,D_{2i+1}=k)\}$$
$$= \sum_{j>0} \sum_{k>0} \{pr(D_{2i-1}=j,D_{2i+1}=k|D_0=0,D_n=m)\ \alpha(x,y,j,k) + pr(D_{2i-1}=-j,D_{2i+1}=-k$$
$$|D_0=0,D_n=m)\ \alpha(x,y,-j,-k)\}$$
$$+ \sum_{j>0} \sum_{k<0} \{pr(D_{2i-1}=j,D_{2i+1}=k|D_0=0,D_n=m)\ \alpha(x,y,j,k) + pr(D_{2i-1}=-j,D_{2i+1}=-k$$
$$|D_0=0,D_n=m)\ \alpha(x,y,-j,-k)\}$$

the second equality obtained using the homogeneity of D_0, D_1, ... By Lemma 6.2(ii) the second double summation equals 0, and now letting $D_n = m = 0$ and by Lemma 6.1 and Corollary 6.1, we have

$$\beta = \sum_{j>0} \sum_{k>0} pr(D_{2i-1}=j,D_{2i+1}=k|D_0=0,D_n=0)\{\alpha(x,y,j,k) + \alpha(x,y,-j,-k)\}$$
$$= \sum_{j>0} \sum_{k>0} pr(D_{2i-1}=j,D_{2i+1}=k|D_0=0,D_n=0)\{\alpha(x,y,j,k) + \alpha(1-x,1-y,j,k)\}$$

where we used Lemma 6.2(iii). But since $\alpha(x,y,j,k) + \alpha(1-x,1-y,j,k) = 0$ for every x, $y \in \{0,1\}$ and j and k odd, part (ii) of Theorem 2.1 is proved. ||

Proof of Corollary 2.1. Let $(t_1,\ldots,t_n)$ with $t_j \in \{0,1\}$ and $2\sum_{j=1}^{n} t_j - n = m$. Then, by letting $J_i = \{1,\ldots,2i-2,2i+1,\ldots,n\}$,

$$pr\{\bigcap_{j=1}^{n}(T_j=t_j)|D_0=0,D_n=m)\} = pr\{\bigcap_{j\in J_i}(T_j=t_j)|D_0=0,D_n=m\}pr\{T_{2i-1}=t_{2i-1},T_{2i}=t_{2i}|D_0=0,$$

$$\bigcap_{j\in J_i}(T_j=t_j),D_n=m\}.$$

By the Markov property of $D_0,D_1,\ldots$ and using the result in the proof of Theorem 2.1 which states that $pr(T_{2i-1}=x,T_{2i}=y|D_{2i-2}=j,D_{2i}=k) = pr(T_{2i-1}=y,T_{2i}=x|D_{2i-2}=j,D_{2i}=k)$ for every j and k even, it follows that

$$pr(T_{2i-1}=t_{2i-1},T_{2i}=t_{2i}|D_0=0,\bigcap_{j\in J_i}(T_j=t_j),D_n=m) = pr(T_{2i-1}=t_{2i},T_{2i}=t_{2i-1}|D_0=0,$$

$$\bigcap_{j\in J_i}(T_j=t_j),D_n=m),$$

hence

$$pr(\bigcap_{j=1}^{n}(T_j=t_j)|D_0=0,D_n=m) = pr\{\bigcap_{j\in J_i}(T_j=t_j),T_{2i-1}=t_{2i},T_{2i}=t_{2i-1}|D_0=0,D_n=m\}. \quad ||$$

Proof of Theorem 2.2: Define

$$\beta = pr(T_{2i+1}=1|D_0=0,D_n=m) - pr(T_{2i}=1|D_0=0,D_n=m).$$

Then, by the Markov property of D_0, D_1, ... we have

$$\beta = E_{0,m}\{pr(T_{2i+1}=1|D_{2i-1},D_{2i+1}) - pr(T_{2i}=1|D_{2i-1},D_{2i+1})\}. \tag{6.1}$$

Using the homogeneity of D_0, D_1, ... and (2.1) we obtain

$$\mathrm{pr}(T_{2i+1}=1|D_{2i-1}=j,D_{2i+1}=j) - \mathrm{pr}(T_{2i}=1|D_{2i-1}=j,D_{2i+1}=j)$$

$$= \mathrm{pr}(T_2=1|D_0=j,D_2=j) - \mathrm{pr}(T_1=1|D_0=j,D_2=j)$$

$$= \begin{cases} 0 & \text{if } j = 3, 5, \ldots \\ C_j(p^{1/2} - pq) & \text{if } j = 1 \\ C_j(pq - p^{1/2}) & \text{if } j = -1 \\ 0 & \text{if } j = -3, -5, \ldots \end{cases}$$

where $C_j = (P^2_{j,j})^{-1}$. By Corollary 6.1 note that $C_1 = C_{-1}$. Since the relevant values of D_{2i-1} in (6.1) are odd integers, and noting that (6.1) equals zero whenever $D_{2i-1} \neq D_{2i+1}$, it follows that

$$\beta = C_1(p^{1/2} - pq)\{\mathrm{pr}(D_{2i-1}=1,D_{2i+1}=1|D_0=0,D_n=m)$$

$$- \mathrm{pr}(D_{2i-1}=-1,D_{2i+1}=-1|D_0=0,D_n=m)\}.$$

By an application of Lemma 6.1, we obtain

$$\beta = C_1(p^{1/2} - pq)(P^n_{0,m})^{-1}\mathrm{pr}(D_{2i-1}=1,D_{2i+1}=1|D_0=0)\{P^{n-2i}_{1,m}-P^{n-2i}_{-1,m}\} .$$

It follows that $\beta(\geq,=,\leq)0$ according to whether $m(>,=,<)0$ respectively. ||

<u>Proof of Theorem 3.1:</u> Using (3.1) we have

$$\pi_m\mu^n_{i,m} = \mathrm{pr}(T_i=1,D_n=m) = \mathrm{pr}(T_1=1,D_{n-i+1}=m) = \pi_m\mu^{n-i+1}_{1,m}$$

which proves (i). Similarly,

$$\pi_m E(T_iT_{i+j}|D_n=m) = \mathrm{pr}(T_i=1,T_{i+j}=1,D_n=m) = \mathrm{pr}(T_1=1,T_{1+j}=1,D_{n-i+1}=m)$$

$$= \pi_m E(T_1T_{1+j}|D_{n-i+1}=m)$$

so that

$$\sigma^n_{ii+j,m} = E(T_iT_{i+j}|D_n=m) - \mu^n_{i,m}\mu^n_{i+j,m}$$

$$= E(T_1T_{1+j}|D_{n-i+1}=m) - \mu^{n-i+1}_{1,m}\mu^{n-i+1}_{1+j,m} = \sigma^{n-i+1}_{11+j,m} . \qquad \|$$

Since the proofs of Theorems 3.2 and 3.3 are similar, we present only the latter.

Proof of Theorem 3.3: By the assumed stationarity,

$$\pi_m E(T_1T_{1+j}|D_n=m) = pr(T_1=1,T_{1+j}=1,D_n=m)$$

$$= \gamma_{m-1}pr(T_1=1,T_{1+j}=1,D_{n-1}=m-1) + (1-\gamma_{m+1})pr(T_1=1,T_{1+j}=1,D_{n-1}=m+1)$$

$$= \gamma_{m-1}\pi_{m-1}E(T_1T_{1+j}|D_{n-1}=m-1) + (1-\gamma_{m+1})\pi_{m+1}E(T_1T_{1+j}|D_{n-1}=m+1).$$

The recursion equation is then obtained by letting $L^k_m = \pi_m E(T_1T_{1+j}|D_k=m)$. The initial and boundary conditions follow from

$$L^{1+j}_m = pr(T_1=1,T_{1+j}=1,D_{1+j}=m)$$

$$= pr(D_j=m-1)pr(T_1=1|D_j=m-1)pr(T_{1+j}=1,D_{1+j}=m|D_j=m-1) = \pi_{m-1}\mu^j_{1,m-1}\gamma_{m-1}. \qquad \|$$

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